General

Guideline Title

Bone health and bone-targeted therapies for prostate cancer.

Bibliographic Source(s)

Alibhai S, Zukotynski K, Walker-Dilks C, Emmenegger U, Finelli A, Morgan S, Hotte S, Winquist E, Genitourinary Cancer Disease Site Group. Bone health and bone-targeted therapies for prostate cancer. Toronto (ON): Cancer Care Ontario (CCO); 2016 Sep 23. 123 p. (Program in Evidence-based Care Guideline; no. 3-14v2). [130 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Question 1

Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving androgen deprivation therapy (ADT)?

Recommendation 1

For men with prostate cancer at high risk of fracture (with or without bone metastases) receiving ADT, denosumab at the osteoporosis-indicated dosage should be considered to reduce the risk of fracture. In situations or jurisdictions where denosumab is contraindicated or not available, a bisphosphonate is a reasonable option.

Question 2

Can therapeutic interventions prevent bone metastases in men with prostate cancer?

Recommendation 2a

In men with high-risk localized prostate cancer, bisphosphonates are not recommended to reduce the risk of first bone metastasis.

Recommendation 2b

In men with nonmetastatic castration-resistant prostate cancer (CRPC), denosumab at the bone metastasis-indicated dosage is not recommended to reduce the risk of first bone metastasis.

Question 3

Can bone-targeted therapies reduce the incidence of skeletal-related events (SREs), reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?

Recommendation 3a

In men with metastatic CRPC (mCRPC), either zoledronic acid (ZA) (minimally symptomatic or asymptomatic disease) or denosumab (disease independent of symptoms) (both at bone metastasis-indicated dosages) is recommended for preventing or delaying SREs. Insufficient evidence exists to make a recommendation with respect to men with castration-sensitive prostate cancer and bone metastasis.

Recommendation 3b

In men with symptomatic mCRPC and bone pain, radium (Ra)-223 should be considered for reducing symptomatic skeletal events and improving health-related quality of life.

Recommendation 3c

In men with mCRPC and bone pain, radiopharmaceuticals or intravenous (IV) bisphosphonates may be considered for pain palliation.

Question 4

Can bone-targeted therapies improve overall survival in men with established prostate cancer and bone metastases?

Recommendation 4

In men with symptomatic mCRPC, Ra-223 is recommended to extend overall survival.

Refer to Table 1-1 in the original guideline document for recommended dosages of medications.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Prostate cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Prevention

Treatment

Clinical Specialty

Endocrinology

Geriatrics

Nuclear Medicine

Oncology

Pharmacology

Radiation Oncology

Radiology

Urology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the effectiveness of therapies targeting bone across all stages of prostate cancer

Target Population

Men with prostate cancer

Interventions and Practices Considered

1. Denosumab
2. Bisphosphonates (e.g., zoledronic acid)
3. Radiopharmaceuticals, including radium (Ra)-223

Major Outcomes Considered

- Bone mineral density (BMD)/osteoporosis
- Risk of fracture
- Skeletal-related events
- Pain
- Time to first bone metastasis
- Patient-reported quality of life
- Overall survival
- Adverse effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines:

- Practice guideline databases:
  - Inventory of Cancer Guidelines
  - National Guideline Clearinghouse
- Guideline developer Web sites:
  - National Institute for Health and Care Excellence (NICE [UK])
  - Scottish Intercollegiate Guidelines Network (SIGN [UK])
  - National Comprehensive Cancer Network (NCCN [US])

A search for existing guidelines for adaptation or endorsement was conducted and no comprehensive guidelines that covered all types of targeted therapies for bone health were found. A search of the primary literature was required.

Search for Existing Systematic Reviews

Systematic reviews were identified by searching MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews. The searches for systematic reviews done in MEDLINE and EMBASE were combined with those performed for primary literature.

Identified systematic reviews were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. The results of the AMSTAR assessment were used to determine whether or not an existing review could be incorporated as part of the evidentiary base.

Any identified reviews that did not meet the criteria above, whose AMSTAR assessment indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base were reported in the reference list, but not further described or discussed.

Literature Search Strategy

A primary literature search was conducted to ensure the retrieval of the latest studies on bone-targeted therapies. Literature searches were performed in the MEDLINE, EMBASE, and Cochrane Library databases to identify primary studies and existing systematic reviews, and the annual meeting proceedings of American Society of Clinical Oncology (ASCO) and the American Urological Association were searched for conference abstracts. MEDLINE was searched in Ovid from 1946 to January 2016 (Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® <1946 to Present>). EMBASE was searched in Ovid from 1980 to January 2016 (EMBASE 1996 to 2016 Week 4).

The literature searches in MEDLINE and EMBASE combined methods terms for meta-analyses, systematic reviews, and randomized controlled trials (RCTs) with terms describing prostate cancer, bone health, and interventions. The full search strategies are found in Appendix 2 in the original guideline document.

Study Selection Criteria and Process

Selected studies were required to meet the following inclusion criteria:

- RCTs or systematic reviews (with or without meta-analysis) containing RCTs
- The study population consisted of men with prostate cancer at any stage. In studies with mixed populations (i.e., including patients with primary cancer sites other than prostate), the data had to be reported separately for prostate cancer patients to be eligible for inclusion.
- The intervention involved therapies directed at improving bone health in nonmetastatic patients or reducing the outcomes associated with prostate cancer metastatic to bone (drug, supplement, or lifestyle modification) alone or in combination and was compared with placebo, no treatment, or other agents.

A review of the titles and abstracts that resulted from the search was conducted by one reviewer. For those items that warranted full-text review, the reviewer reviewed each item and discussed with the lead authors to confirm the final study selections. All data were audited by a second, independent auditor.

Refer to the "Results" section of the original guideline document for information on studies retrieved through the literature searches.

Number of Source Documents

The final number of included papers was 93 (15 systematic reviews and 78 reports of 72 randomized controlled trials [RCTs]).

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one Working Group member with assistance from the two lead authors. The methodological quality characteristics of the included randomized controlled trials (RCTs) were recorded. These included allocation concealment, blinding, intention-to-treat analysis, funding, patient follow-up, statistical power and sample size, baseline characteristics balance, and early termination. Androgen deprivation therapy (ADT) status, intervention groups and numbers of patients, dosage schedule, follow-up periods, and outcome measures were recorded for each study.

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration. If the hazard ratio (HR) or its standard error were not reported, they were derived from other information reported in the study, if possible, using the methods described by Parmar et al. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in RevMan was used.

Statistical heterogeneity would be calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method for assessing the quality of aggregate evidence was used for each comparison. The outcomes were rated for their importance for decision-making by the Working Group members. Four factors were assessed for each outcome in each comparison. These included the risk of bias, inconsistency, indirectness, and imprecision. Risk of bias was assessed by the presence/absence of the methodologic quality characteristics described above.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Developers

This guideline was undertaken by the Program in Evidence-Based Care (PEBC) at the request of the Genitourinary Cancer Disease Site Group (GU DSG). This group was comprised of four medical oncologists, nine radiation oncologists, seven urologist/surgical oncologists, one pathologist, and one PEBC methodologist (see Appendix 1 in the original guideline document for membership).

The project was led by a small Working Group, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group members included a geriatrician with expertise in both genitourinary cancer and bone health in men and a radiologist/nuclear medicine physician with expertise in prostate cancer imaging and targeted radionuclide therapy. All members contributed to final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Other members of the GU DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.

Guideline Development Methods

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. This process includes a systematic review, interpretation of the evidence by the Working Group, resulting recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines for Research and Evaluation (AGREE) framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the PEBC Document Assessment and Review Protocol (see the "Availability of Companion Documents" field). PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Research Questions

1. Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving ADT?
2. Can therapeutic interventions prevent bone metastases in men with prostate cancer?
3. Can bone-targeted therapies reduce the incidence of SREs, reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?
4. Can bone-targeted therapies improve overall survival in men with prostate cancer?

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the Guideline Development Group (GDG) Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the targeted peer review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through professional consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

See Section 5 in the original guideline document for further discussion of the internal and external guideline review process and results.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by systematic reviews and randomized controlled trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Therapeutic interventions and bone-targeted therapies reduce and/or alleviate bone complications related to prostate cancer.

Potential Harms

Adverse effects of medications and radiopharmaceuticals. Refer to Appendix 23 in the original guideline document for detailed description of side effects of these and other relevant drugs.

Qualifying Statements

Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.
- See the original guideline document for qualifying statements related to each recommendation.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Considerations

The Working Group members consider these recommendations to represent a current standard of care and believe they will be feasible to implement. They believe the outcomes valued by clinicians will align with the outcomes valued by patients and most patients and healthcare providers will view the recommendations as acceptable. The Working Group members also believe that these recommendations will not require additional training for the providers or necessitate a significant change to the current health system.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alibhai S, Zukotynski K, Walker-Dilks C, Emmenegger U, Finelli A, Morgan S, Hotte S, Winquist E, Genitourinary Cancer Disease Site Group. Bone health and bone-targeted therapies for prostate cancer. Toronto (ON): Cancer Care Ontario (CCO); 2016 Sep 23. 123 p. (Program in Evidence-based Care Guideline; no. 3-14v2). [130 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Sep 23

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Genitourinary Cancer Disease Site Group

Guideline Development Group (GDG) Working Group

Composition of Group That Authored the Guideline

Working Group Members: S. Alibhai, K. Zukotynski, C. Walker-Dilks, U. Emmenegger, A. Finelli, S. Morgan, S. Hotte, E. Winquist

Financial Disclosures/Conflicts of Interest

Conflict of interest declarations for all Guideline Development Group (GDG) members are summarized in Appendix 1 of the original guideline document, and were managed in accordance with the Program in Evidence-Based Care (PEBC) Conflict of Interest Policy .

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site .

Availability of Companion Documents

The following are available:

- Alibhai S, Zukotynski K, Walker-Dilks C, Emmenegger U, Finelli A, Morgan S, Hotte S, Winquist E, Genitourinary Cancer Disease Site Group. Bone health and bone-targeted therapies for prostate cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2016 Sep 23. 7 p. (Program in Evidence-based Care Guideline; no. 3-14v2). Available from the Cancer Care Ontario (CCO)Web site .
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the CCO Web site .
- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site .
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the CCO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 6, 2016.

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